Organic Process Research & Development **2007**, *11*, 178–189

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during July to September 2006

Summary

This latest review contains summaries of 23 patents from an original list of 471 that covers a very wide range of topics. The use of phase transfer catalysts and two-phase systems has been described in a number of cases. Examples are improved processes for preparing candesartan cilexetil, a drug used to treat hypertension, cizolirtine a new analgesic in clinical trials, and ranelic acid that is used to treat osteoporosis. On the subject of phases a patent describes the advantages of using two-phase reaction system over a single-phase system. The patent describes the first two-phase enzymatic reaction for the synthesis of an intermediate used to make the decongestant ephedrine. Also on the subject of phases is a patent covering the reaction of large hydrophobic molecules with small hydrophilic ones. The use of detergent-type materials such as linear alkyl benzene sulfonates assists the reaction.

The subject of polymorphs should always be in the minds of development chemists. One patent describes the existence of 13 new polymorphs of the drug valsartan. This is a frighteningly large number since there had not been reports of any polymorphic forms of this compound. The development of drugs to treat various cancers is covered, and one describes a range of novel intermediates for the synthesis of tubulin inhibitors, while another focuses on new intermediates for making neplanocin A. A novel method of making the gastric ulcer drug pantoprazole makes use of an oxidation reaction employing an inexpensive reagent peracid that is commonly found in cosmetic or detergent formulations.

Reactions at temperatures below −40 °C are difficult and expensive to carry out on large scale. Temperatures above −40 °C are fairly easy to achieve, and a process for carrying out electrophilic substitutions to make methylserines and methylcysteine salts is described that takes place at −25 °C. A one-pot process for making an antiepileptic agent is described, but it uses dichloroethane and so has potential for high environmental impact. A method for making the fungicide azoxystrobin employs the strategy of building up the molecular structure from the end opposite to that used in previous syntheses. Instead of starting with a methoxyacrylate group and then adding a pyrimidinyloxy group, the new method starts from the opposite direction. Nonsteroidal antiinflammatory drugs are in the news for the wrong reasons and they are the subject of two patents. One describes a new method of making the established drug ibuprofen and the other a novel range of benzoxazinone derivatives. A method of manufacturing an opioid analgesic is described that involves a novel direct oxidation step of thebaine salts obtained from poppy straw. The method compares very well with earlier indirect oxidations.

The high incidence of heart diseases means an increasing need for better and safer drugs for treatment. Improved methods are described for making intermediates used for the synthesis of ivabradine and also for candesartan cilexetil. Two patents are included in this selection that have very wide-ranging claims but limited examples. One claims to be suitable for dehydrating organic compounds to make unsaturated compounds, and the other is an improved crystallisation method. The first patent has an example only for making PhCN from an oxime, while the second is aimed at the bulk chemical terephthalic acid. The process uses hydrocyclones to separate crystals from a slurry and is an interesting technique that may have applications in other crystallisations. The preparation of an aqueous salt-free hydroxylamine solution is important in the electronics industry, and a new method could be of interest to development chemists. There may, however, be safety issues. Some of the patents reviewed have details of large-scale examples, indicating that the processes may be near or at commercial operation. However, this is speculation on the part of this reviewer, and there is no legal or commercial significance in the choice of patents listed although it is hoped that readers find some interesting techniques or methods. The advantages noted are those claimed in the patent unless this reviewer has personal knowledge of the subject.

Patent No. U.S. 7,071,336

Assignee: Aura Pharmaceuticals, Palatine, Illinois

Title or Subject: Process for the Manufacture of Opioid Analgesics

This patent is specifically aimed at the production of oxycodone, **3**, a well-known narcotic used in pain management. The process to make **3** involves the oxidation of thebaine **1** to form 14-hydroxycodeinone, **2**, and this is subsequently reduced to **3** (Scheme 1). The patent describes a process using **1** or preferably a chiral thebaine salt component obtained from concentrated poppy straw. A variety of methods have been used to oxidise **1**, and some of these are direct, while others are indirect. The current patent describes a direct oxidation step of the

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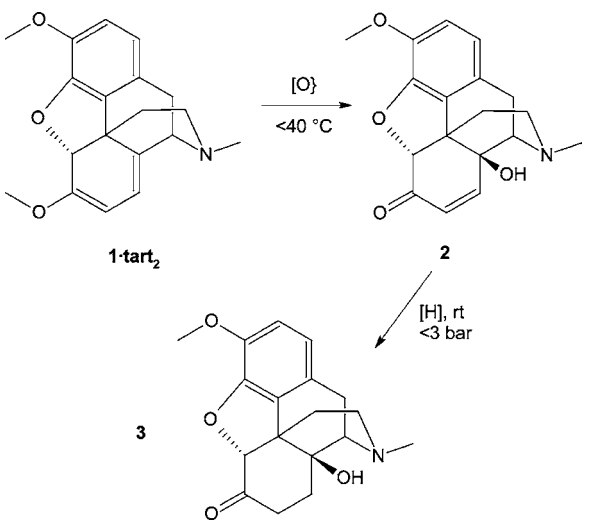
bitartrate salt of **1** (**1**·**tart**$_2$) using HCO_2H/H_2O_2 or $MeCO_2H/H_2O_2$ as oxidising agents in water, MeOH, or *i*-PrOH. The oxidation is carried out below 45 °C over a period of 3−5 h.

The reduction of **2** to **3** is claimed to be possible with a range of noble metal catalysts although examples use either Pd/C or $Pd/BaSO_4$ catalysts at ambient temperature and <3 bar pressure. The overall yield of **3** is good with 93% of **2** recovered in one example of the first step and 91% in the second step.

The patent also describes the preparation of the HCl salt of **3** and of the bitartrate salt of **1** via *N*-carboethoxynorthebaine.

Scheme 1



Advantages

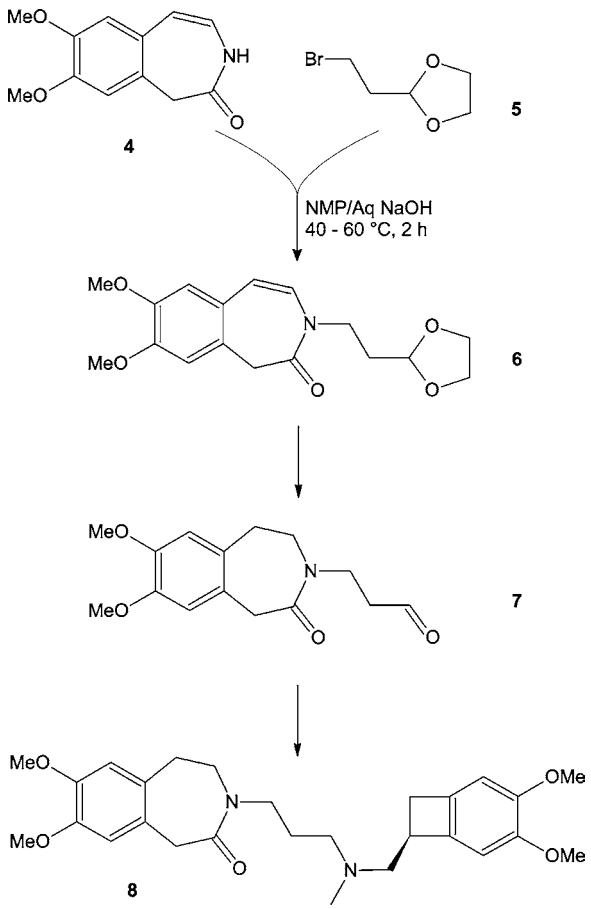
The process uses mild conditions for the oxidation, thereby giving a high yield and selectivity.

Patent No. U.S. 7,074,920

Assignee: Les Laboratories Servier, Courbevoie, France
Title or Subject: Process for Intermediates in the Synthesis of Ivabradine

Ivabradine **8** and its acid salts have bradycardic properties and are used to treat a variety of heart problems. The patent is specifically aimed at the production of **6**, an intermediate used to prepare **7** that is then used to produce **8**. Alternative methods of preparing **8** are described and these usually involve reaction between N-alkylated compounds similar to **6**. Acetals or chloropropyl groups have been used, but the problems in using these give low yields of **8**. The current patent introduces the dioxolane group by reaction of **4** with **5** to give **6** in an 87% yield. **6** is then converted to the aldehyde **7** by hydrogenation and deprotection although no details of these steps are given. An alternative method of preparing **6** from **4** and **5** is by using K_2CO_3. However, this requires a higher temperature (130 °C) and gives a lower yield (80%) of **6**. It is stated in the patent that this reaction of **4** and **5** is surprising because lactams usually require stronger bases to cause deprotonation.

Scheme 2



Advantages

The process gives a more selective method of producing the desired intermediate **6** under mild conditions than would normally be required.

Patent No. U.S. 7,074,966

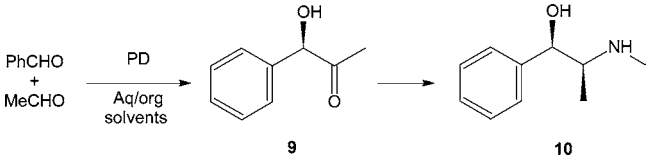
Assignee: BASF AG, Ludwigshafen, Germany
Title or Subject: Enzymatic Process for Producing R-Phenylacetylcarbinol in a Two-Phase System

The compound **9** is a precursor for the synthesis of **10** that is used as a decongestant and known as ephedrine. A fermentation method for producing **9** was described in 1932 and was in operation until a few years ago. It is also known that the enzyme pyruvate decarboxylase (PD) is responsible for the synthesis of **9** in microorganisms. This patent discloses the first two-phase enzymatic system for the synthesis of **9** although a one-phase system has previously been described.

Scheme 3 shows the basis of the process, and it involves the reaction of PhCHO with MeCHO in a buffered solvent mixture of water and an alkanol in the presence of PC derived from a microorganism such as *Zymomonas mobilis* or *Candida utilis*. The solvent system is mixed to form an

emulsion using a suitable method of agitation. It is also possible to carry out the reaction without the need to form an emulsion of the two by gently mixing the two liquids. Preferred alcohols are octanol or nonanol or a mixture of the two.

Scheme 3



The patent provides data showing the use of several different solvents, and alcohols gave the best results. It is interesting to note that using MTBE as the organic solvent enhanced the stability of the enzyme although the productivity of **9** was not as high as when alcohols were used. The stabilisation is partly attributed to the ability of MTBE to reduce the amount of water bound to the enzyme. This is claimed to stabilise the enzyme by allowing a more stable folded configuration to be achieved.

Advantages

The use of two-phase systems appears to enhance the productivity and isolation of product when compared with single-phase processes.

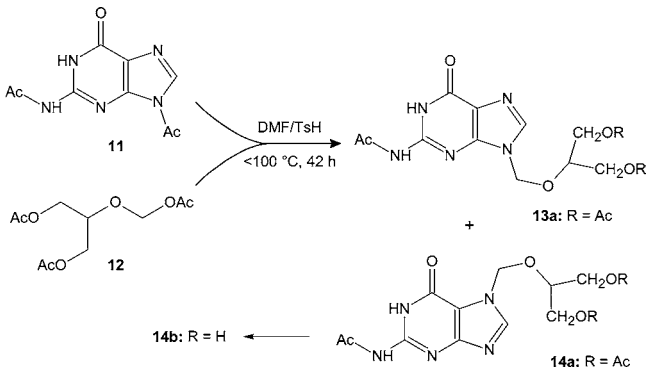
Patent No. U.S. 7,078,524

Assignee: Ranbaxy Laboratories Limited, Haryana, India
Title or Subject: Process for the Synthesis of Ganciclovir

The title compound **14b** is an antiviral agent used to treat several viruses of the Herpes family. A difficulty with synthesising a purine compound such as **14b** is that the undesirable 7-isomer **13b** (R = H) is also formed, and since this is thermodynamically favoured, a separation of the two compounds is needed. Thus, attempts to make **14b** also produce **13b** often at up to 35%, and although the two isomers have differing solubility, the separation may be difficult. This patent describes a procedure for the in situ conversion of the undesired isomer to the desired one and subsequent separation of the product. Scheme 4 shows the basis of the method used. It involves the preparation of a mixture of the two compounds **13a** and **14a** from diacetyl guanine **11** and **12**. After reaction the solvent is removed, the residue, an oily syrup, is dissolved in hot MeOH, and on cooling the 7-isomer **13a** is obtained by crystallisation. The filtrate contains the 9-isomer **14a** and this is obtained by crystallisation from a MeOH/PhMe mixture. Alternatively, less desirable chlorinated solvents can be used in place of PhMe.

If the recovered **13a** is treated with **11** and **12**, some of it is converted to **14a**. Extraction of the reaction product with MeOH and crystallisation then affords **13a. 14a** is obtained from the filtrate as described above. The final product **14b** is obtained by hydrolysis of **14a**.

Scheme 4



In general it is found that the 7-isomer **13a** is preferably separated from lower alcohol solvents, whereas the 9-isomer **14a** is obtained from mixture of MeOH and water-immiscible solvents such as PhMe or chlorinated solvents.

Advantages

The process allows recovery of the undesired intermediate isomer and its conversion to the desired isomer.

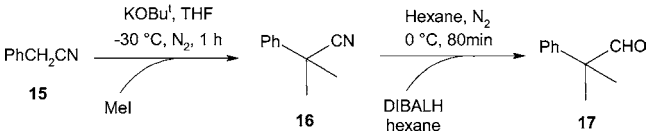
Patent No. U.S. 7,078,572

Assignee: Wyeth Holdings Corporation, Madison, New Jersey
Title or Subject: Process for Intermediates used in the Synthesis of Tubulin Inhibitors

Tubulin inhibitors are used in treating various cancers. The claims of this patent focus on the production of the aldehyde **17** that is used in the synthesis of **23**. It is this latter compound that is a key intermediate for synthesising tubulin inhibitors. The patent does provide extensive discussion on the synthesis of **23** although there are no claims related to the synthetic methods described and they may be the subject of other patents.

The synthesis of **17** is shown in Scheme 5 and is quite straightforward involving alkylation of **15** with MeI to give **16** that is reduced using DIBALH. Alternative reducing agents can be used such as Sn/HCl or $LiAlH_4$.

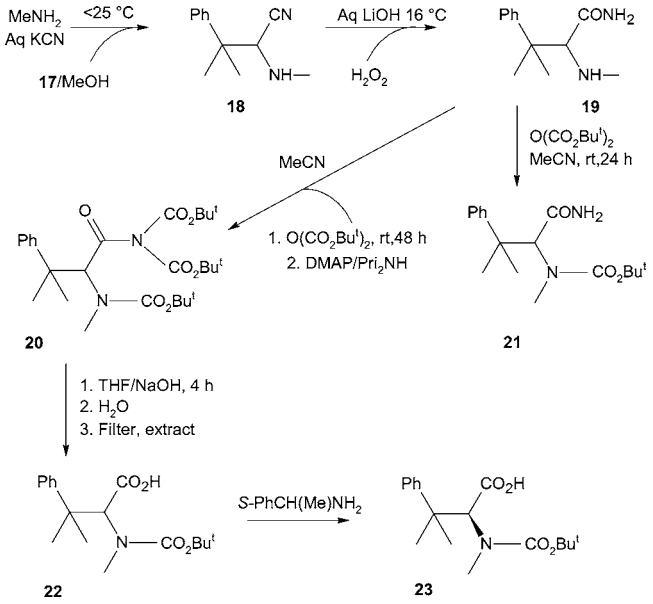
Scheme 5



The aldehyde **17** is used to prepare **23** by the route shown in Scheme 6. The reaction proceeds via the amide **19** that is produced by reduction of the nitrile **18**. The amine group in **19** is then protected by conversion to the *tris*-BOC compound **20** by using the $(BOC)_2O$. It is also

possible to convert **19** to the mono-BOC compound **21**, and this can be isolated if required or converted to **20**. Base hydrolysis of **20** removes the amido BOC groups, giving **22**, and this is resolved byusing amine resolving agents such as *S*-PhCH(Me)NH_2 to obtain **23**.

Scheme 6



The patent also describes alternative schemes to produce compounds related to **23** in which more complex groups replace the CO_2H moiety in **23**. This is clearly part of a very extensive programme of work in this area, and interested readers are encouraged to consult the patent.

Advantages

The patent opens up an area of work in a field where there is much activity in developing novel drugs for treatment of cancers.

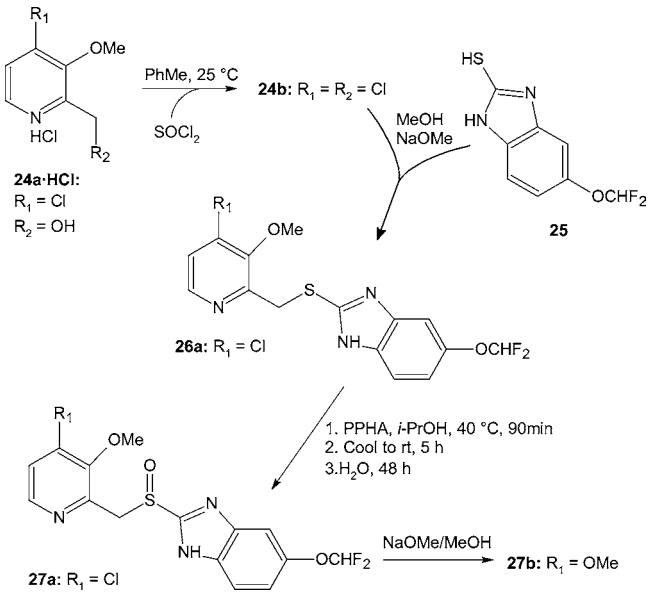
Patent No. U.S. 7,081,534

Assignee: Dipharma S.p.A., Mereto di Tomba, Italy

Title or Subject: Process for the Preparation of Pantoprazole and its Salts

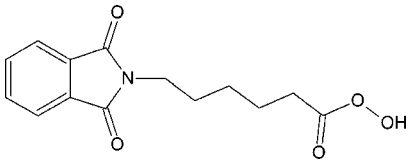
The sodium salt of pantoprazole **27b** is used to treat gastric ulcers and a patent on this compound was reviewed recently (*Org. Process Res. Dev.* **2006**, *10*, 866). A key step in the preparation of **27b** and its analogues involves the oxidation of the thioether **26a** to sulfinyl compound **27a**. Several oxidising methods have been used, and these are said to suffer various problems on a commercial scale. This patent addresses this oxidation step using the oxidising agent ϵ-phthalimidoperhexanoic acid (PPHA) and Scheme 7 shows the reaction sequence for preparing **27b**. PPHA is a commercially available reagent that is a stable solid. It is used primarily in cosmetic formulations and household detergents and thus is safe to handle.

Scheme 7



The initial step involves the production of the chloromethylpyridine **24b** by chlorination of **24a** using $SOCl_2$. This is then reacted with the thiol **25** to give the thioether **26a** in about 83% yield. The key oxidation step of **26a** to **27a** is then carried out using PPHA. This can be done in *i*-PrOH using the purified **26a** or by using the PhMe reaction solution from the previous step. In the final step the Cl group in **27a** is replaced using NaOMe to give **27b** that is recovered as the sesquihydrate of the Na salt in 71% yield.

PPHA



Advantages

The process uses a safe and readily available oxidising agent and this is likely to improve the economics and operability of the process.

Patent No. U.S. 7,081,537

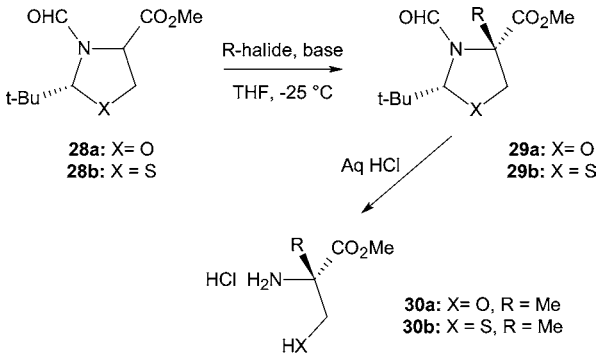
Assignee: Consortium fur Elektrochemische Industrie GmbH

Title or Subject: Process for the Electrophilic Substitution of Thiazolidines or Oxazolidines

This patent is aimed at improving the diastereoselectivity of electrophilic substitution reactions to give compounds such as **29a** or **29b**. Alternative processes for carrying out this type of reaction are said to give poor yields and require temperatures between −40 °C and

−90 °C that are costly to achieve. The use of such temperatures certainly is costly, and the processes described in this patent when carried out at around −25 °C are cheaper to attain. The patent describes a number of reactions that are shown in Scheme 8 from the precursors **28a** and **28b**. There are examples given for each compound, and the reactions are carried out using strong bases such as LHMDS, KOBu^t.

Scheme 8



R = allyl, benzyl, benzoyl, ethyl or methyl

The reaction can be carried out using either the *4R* or *4S* enantiomers and they both give the same product. It is said that it is the stereochemistry of the 2-group that dictates the product configuration. It is stated that selectivity is brought about by an intact, enantiomerically pure, stereogenic centre in the 2-position of the ring. The main use of this reaction appears to be the stereoselective production of HCl salts such as **30a** or **30b** by acid hydrolysis of **29a** or **29b** as shown in Scheme 8. These methylcysteine or methylserine salts have uses in the synthesis of pharmaceuticals.

Advantages

The process employs higher temperatures than alternative procedures, and this means that the process is more suitable for commercial-scale production.

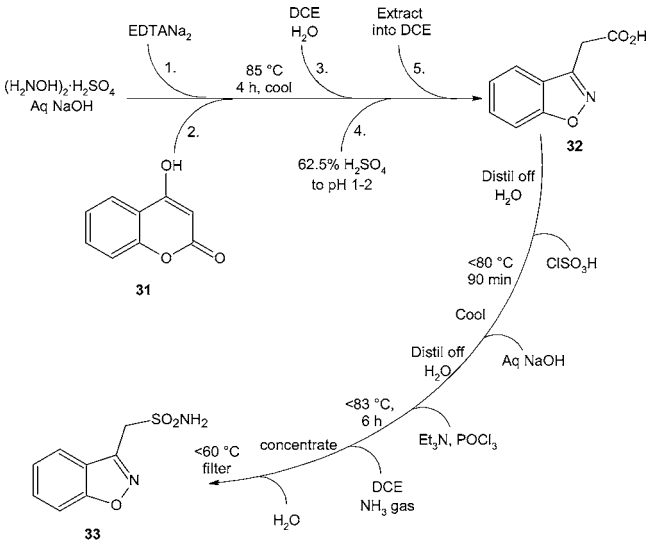
Patent No. U.S. 7,081,539

Assignee: Dainippon Sumitomo Pharma Co., Osaka-Fu, Japan

Title or Subject: One-Pot Process for the Preparation of 1,2-Benzisoxazole-3-methanesulfonamide

The title compound **33** is an antiepileptic agent. Several methods are described for the synthesis of **33**, but none are one-pot processes. The patent describes a process that does not require the isolation of intermediates in the solid form. The process also involves a method of making the intermediate **32** using water as solvent. Scheme 9 summarises the many steps used in this process that initially produces the acid **32** from the readily available **31**. This reaction is carried out in the presence of a chelating agent such as the Na salt of EDTA. This is said to suppress the rapid decomposition of the H_2NOH that can take place unexpectedly if Fe salts are present, and the decomposition can give rise to a large exotherm. Thus, the EDTA salt is used to control the process and make it safer to operate.

Scheme 9



DCE = 1,2 dichloroethane

Advantages

The process uses a readily available starting material in a one-pot process that can be easily controlled. However, the process uses a solvent that is not attractive from an environmental standpoint. The final product is claimed to contain <5 ppm of DCE, and presumably this is below the safe level.

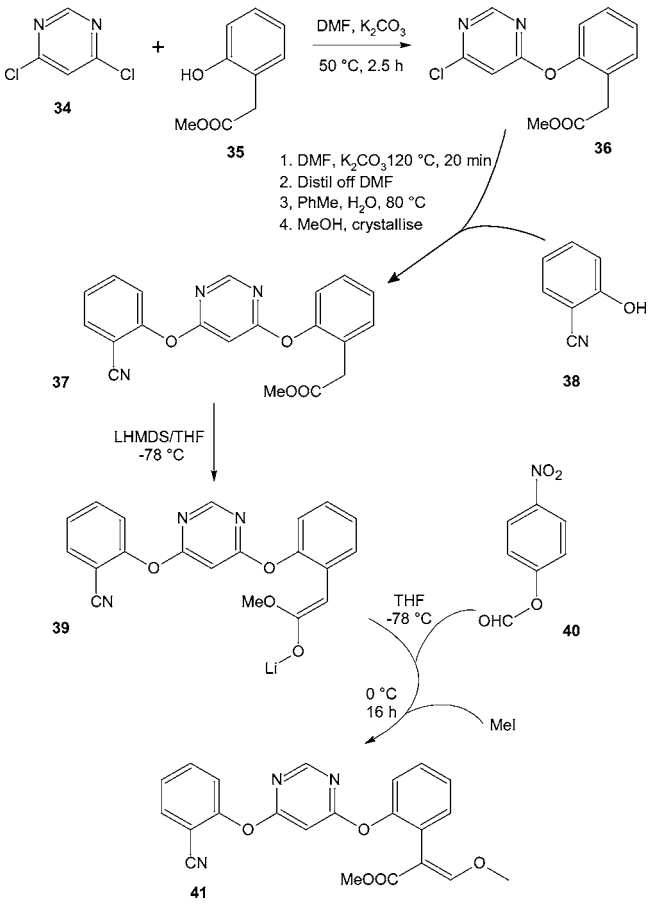
Patent No. U.S. 7,084,272

Assignee: Syngenta Limited, Huddersfield, United Kingdom

Title or Subject: Process for the Preparation of Azoxystrobin and Analogues

Azoxystrobin **41** is an agricultural fungicide that can be made by several different methods. A key aspect of the synthesis is the construction of the methoxyacrylate group. It is claimed that alternative procedures initially construct this group and then add the pyrimidinyloxy group. However, the method employed in this patent is to add the methoxyacrylate group to the previously constructed pyrimidinyloxy structure. Scheme 10 shows the reaction steps developed to build up the pyrimidinyloxy group via **36** and **37**. The Li derivative **39** is then formed by treatment of **37** with LHMDS. Subsequent formylation of **39** with **40** followed by methylation with MeI gives **41**. Unfortunately the yield by NMR and GC/MS is only 10%, and a recovered yield is not stated.

Scheme 10



The patent states that prior to this work there was no indication that lithiated bases could be successfully employed in the formation of **41**. One reason mentioned why prior workers have built the methoxyacrylate group first is that compounds **36** and **37** can undergo a Smiles-type rearrangement in the presence of commonly used bases. This then gives rise to by-products that cannot be converted to the desired product.

Advantages

The patent introduces a novel method of synthesising azoxystrobin, but the yield is very poor; it is unlikely to be a commercially attractive process. The sole purpose of the patent may be to prevent others using this type of method. Such a patent is often known as a blocking patent.

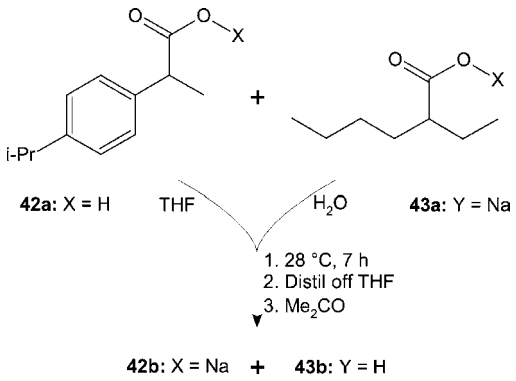
Patent No. U.S. 7,084,294

Assignee: Strides Research and Specialty Chemicals Limited, New Mangalore, India

Title or Subject: Process for Producing Ibuprofen Sodium Dihydrate

Ibuprofen **42a** is widely used as an analgesic and nonsteroidal antiinflammatory drug (NSAID). The acid form of the drug **42a** is very insoluble in water, and hence the Na form **42b** is used since it has a higher bioavailability because it is more soluble. A number of processes are known for producing **42a**, and generic forms of the drug are available because patents have expired. This patent describes a process for preparing **42b** from **42a** by reaction with the Na salt **43a** in THF or EtOH (Scheme 11). After the reaction the solvent is removed by distillation and the mixture poured into Me_2CO. The product is the dihydrate and is recovered by filtration as 99% pure by HPLC. The acid **43b** is removed in the acetone solution and can be recovered and presumably reused after conversion to **43a**.

Scheme 11



Advantages

The patent provides an alternative procedure for preparing this important drug compound.

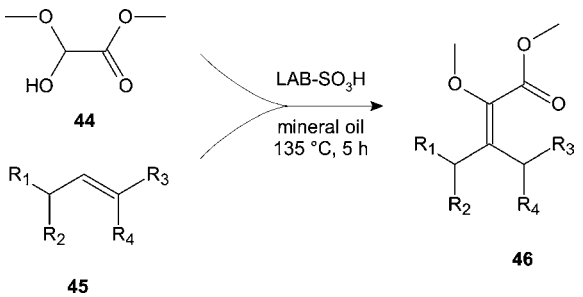
Patent No. U.S. 7,087,558

Assignee: The Lubrizol Corporation, Wickcliffe, Ohio

Title or Subject: Process for Reacting Large Hydrophobic Molecules with Small Hydrophilic Molecules

There are many examples where physically incompatible materials need to be contacted in order for a reaction to be carried out. The limitations in such processes are physical rather than chemical, and if viscous materials are used, then efficient mixing and contacting is even more difficult. To avoid using organic solvents that would need to be removed, this patent uses catalysts with solubilising properties. The patent specifically covers the acid-catalysed Prins-type reaction between **44** and hydrocarbon polymers such as **45** in a mineral oil mixture. The products are used as intermediates in producing lubricating oil additives. Instead of normal mineral acids or MsH as catalysts this process uses linear alkyl benzene (LAB) sulfonic acids since these have solubilising properties. Scheme 12 outlines the process used to make the product **46** where the groups R_1-R_4 represent a variety of polymeric compounds that can contain C═C bonds. The material used in the examples is an ethylene−propylene−ethylidene−norbornadiene terpolymer, and **44** is a commercially available material. After removing volatiles from the mixture the oil solution is used directly as the product.

Scheme 12



Advantages

The procedure using solubilising catalysts allows the process to be carried out without the need to use solvents.

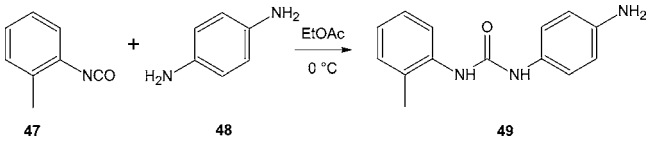
Patent No. U.S. 7,091,242

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: β-Amino Acid Derivatives as Integrin Receptor Antagonists

The compounds of interest in this patent such as **53b** are novel and useful in the treatment of a variety of cell-adhesion-mediated disorders. The patent covers a large number of compounds, and the synthesis of **53b** as a representative example is shown in Scheme 14. The first part of the process shown in Scheme 13 is the synthesis of the urea **49** that is easily produced from the isocyanate **47** and the diamine **48**.

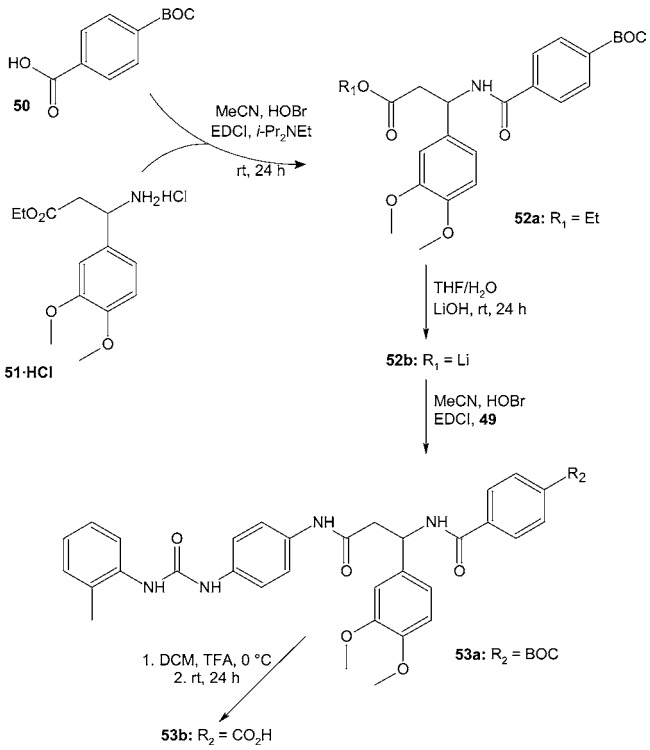
Scheme 13



47 48 49

The next sequence is shown in Scheme 14. The synthesis of **52a** is obtained by coupling of the acid **50** and the amine salt **51·HCl**. This is carried out using EDCI in MeCN containing HOBr and an amine. The Li salt **52b** is then prepared, and this is coupled with **49** to give **53a**. The acid **53b** is formed by treatment of **53a** with TFA in DCM.

Scheme 14



The patent gives basic ^{1}H NMR data for the novel compounds and intermediates. Some data on the effectiveness of the compounds are provided.

Advantages

The patent provides a method of synthesising some novel compounds that have potential pharmaceutical applications.

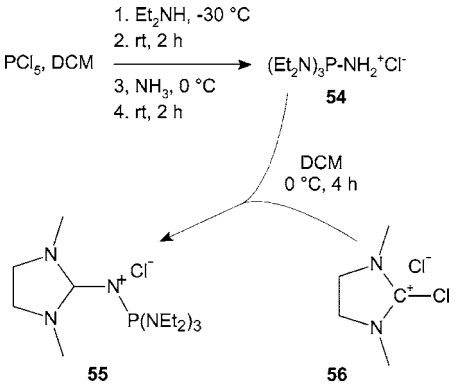
Patent No. U.S. 7,091,362

Assignee: Bayer AG, Leverkusen, Germany

Title or Subject: Process for Preparing Nuclear-Fluorinated Aromatics

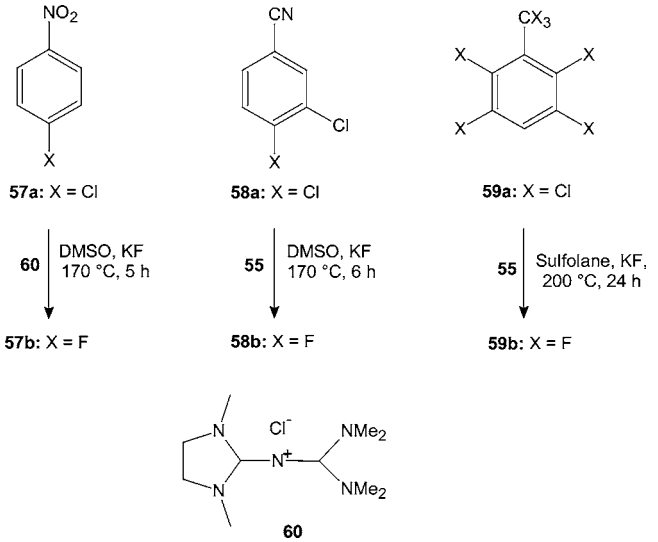
Fluorinated compounds are very useful in pharmaceutical and agrochemical applications. They are often prepared by halide exchange reactions but some of the reagents used are very toxic. In addition high temperatures may be needed when using nonactivated aromatics. This patent describes a method of fluorination of aromatics using KF in conjunction with salts such as **55** and **60**. The two claims of the patent actually relate to the novel compound **55**, and the patent describes its synthesis by the method outlined in Scheme 15. The yields of the products can be as high as 96%.

Scheme 15



The salts **55** and **60** are used in the fluorination of several aromatic compounds, and Scheme 16 summarises some of these. Comparative examples are given that use guanadinium or phosphonium salts without KF. These do not provide such good yields or require more forcing conditions than the methods described in the current patent.

Scheme 16



Advantages

The patent describes novel phosphonium salts that can be used to improve the fluorination of aromatic compounds.

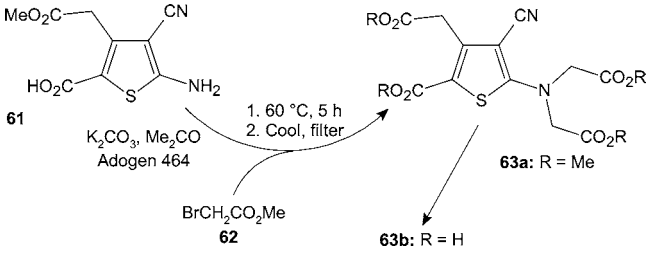
Patent No. U.S. 7,091,364

Assignee: Les Laboratoires Servier, Courbevoie, France

Title or Subject: Process for Synthesising Ranelic Acid Salts and Intermediates

The strontium salt of ranelic acid **63b** (R = H) helps the healing and strengthening of bones especially in older women who may suffer from osteoporosis. The material is approved for use in the United Kingdom, but not yet in the United States, and is available under the name Protelos. This patent describes a method of producing the ester **63a** from which the acid and its salts can be made. Scheme 17 shows the route used to prepare **63a** from **61** and the bromoacetate **62**. The reaction is carried out in the presence of a quaternary ammonium salt. The materials Adogen 464 or Aliquat 336 are being specifically mentioned, and these salts do act as phase transfer reagent catalysts (PTC). The product **63a** is obtained in 85% yield and has a chemical purity of 98%.

Scheme 17



Experiments are described that use several hundred kilos of reagents, and it is assumed that this is the basis for the commercial production of the drug.

Advantages

The process provides a commercial method for synthesis of this drug.

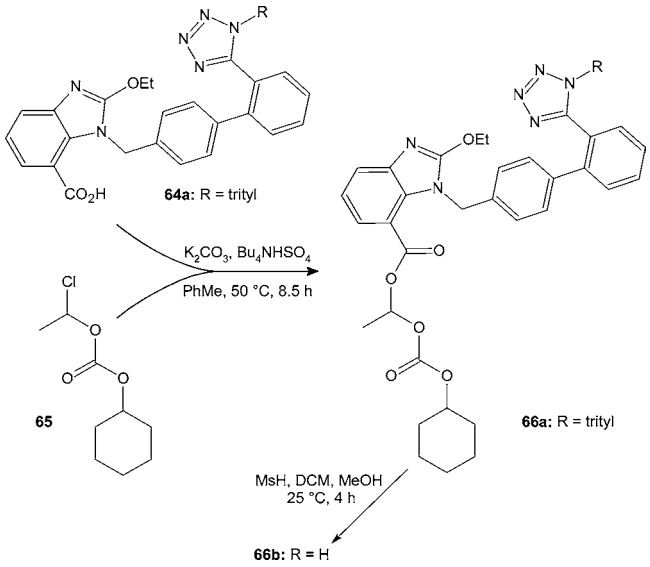
Patent No. U.S. 7,098,342

Assignee: Teva Pharmaceutical Industries Ltd., Petah Tiqva, Israel

Title or Subject: Preparation of Candesartan Cilexetil

Candesartan cilexetil **66b** is an angiotensin receptor blocker used to treat high blood pressure and congestive heart failure. The drug is sold and used as a racemic mixture although it does have a chiral centre. **66b** is usually prepared by removal of the trityl protecting group from the precursor **66a**. This patent describes a method of preparing **66a** and then removing the trityl group using an acid and a PTC. Scheme 18 shows the reactions involved. Initially **66a** is prepared from **64a** and **65** in the presence of an inorganic base and a PTC in a low boiling solvent. The solvent must boil between 80 and 120 °C. The product is obtained in about 67% yield with an HPLC purity of 97.9%. The reaction gives slightly lower purity when a PTC is not used. The final stage of the process is to remove the trityl group using acid catalysts such as HCO_2H, TsH, MsH, or TFA or without using an acid. It is not clear which procedure is preferred since good results appeared to be obtained in all cases.

Scheme 18



Advantages

The patent provides an alternative method of preparing the drug.

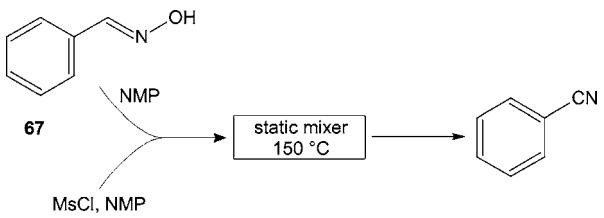
Patent No. U.S. 7,098,357

Assignee: Merck Patent GmbH, Darmstadt, Germany

Title or Subject: Method for Dehydrating Organic Compounds in a Microreactor

The patent claims to be applicable to the production of all types of unsaturated compounds by dehydration. Thus, it includes alkenes from alkanes, amides or aldoximes to give nitriles, and alcohol conversions to alkenes. However, despite the rather grand title of this patent there is only one example provided for the production of PhCN shown in Scheme 19. The process is carried out continuously by mixing a solution of **67** in NMP with MsCl/NMP in a static mixer at 150 °C. The example given is carried out on small scale using 2-mL disposable syringes as feed vessels. The flow rates were set to give a residence time of 3.75 min, and this was sufficient to ensure that the dehydration reaction was completed. Obviously for other reactions, the residence time would need to be adjusted.

Scheme 19



The patent's claims cover almost all the dehydrating agents and reactions that one can imagine. However, if the reaction is indeed suitable for them all, the fact that the microreactor must have a volume <100 μL limits its use.

Advantages

The patent aims to provide a dehydration process that does not involve large volumes of material, thus reducing safety problems. While it does this, it has many limitations.

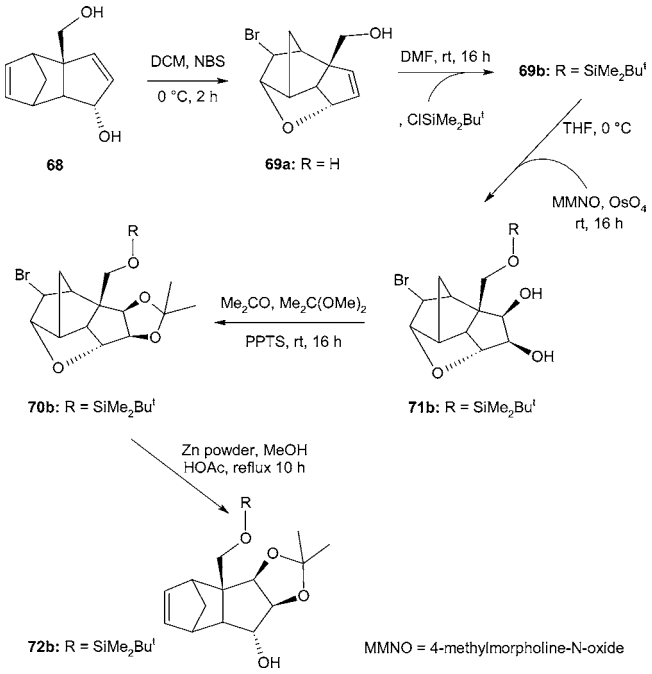
Patent No. U.S. 7,102,018

Assignee: Chisso Corporation, Osaka-Fu, Japan

Title or Subject: Intermediates and Improved Processes for Preparing Neplanocin A

Neplanocin A **77a** is a carbanucleoside with strong antitumour activity. However, it has strong adverse effects, and thus it is not used alone for treating cancer. Improvements in the synthesis of **77a** have been reported, and some have been recently reviewed (*Org. Process Res. Dev.* **2005**, *10*, 866). This patent is an extension of the earlier work from Chisso and covers the compound **72b** that is an intermediate in the synthesis of **77a**. Scheme 20 summarises the route used to prepare **72b**. The first steps are straightforward, and the first key aspect is the selective oxidation of **69b** to give **71b** using OsO_4 and MMNO as the oxygen source. The ketalization of **71b** to give **70b** is carried out using the acetal $(MeO)_2CMe_2$ and PPTS as catalyst. The Br is removed in the next step using Zn to give **72b**.

Scheme 20

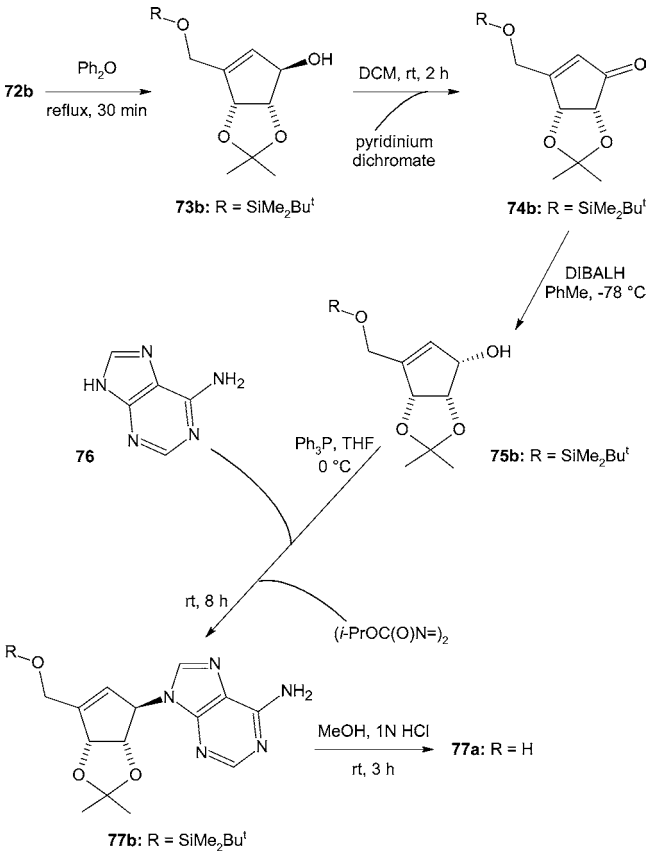


The next key point of the process is the conversion of **72b** to **73b** by a retro-Diels−Alder reaction. **73b** is then converted in two steps to **75b** in which the stereochemistry of the OH is inverted. **75b** then is converted to **77b** in a Mitsunobu reaction in which it is treated with Ph_3P, adenine (**76**), and the azocarboxylate (*i*-PrOC(O)N═)$_2$. In the final stage **77a** is produced by acid hydrolysis of **77b**. The overall yield for the 10-step synthesis of **77a** from **68** is said to be 45%. This compares very well with other routes that give 4% in 13 steps or 12% in 9 steps.

Advantages

The process gives a much higher yield than alternative routes.

Scheme 21



Patent No. U.S. 7,105,078

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Method for Producing a Salt-Free Aqueous Solution of Hydroxylamine

High purity hydroxylamine solutions are used for cleaning purposes in the electronics industry, and these must be free of salts to avoid damage to the circuit boards or silicon wafers. The maximum total salt level is <1 ppm and is often much lower. Hence, there is a need for salt-free solutions of the reagent. The basis of the method is to react a hydroxylammonium salt with a base to give an aqueous mixture containing the salts and the hydroxylamine. This mixture is then separated by distillation. In a continuously operated column water is taken off overhead and the concentrated salt-free aqueous hydroxylamine taken off at an intermediate point. The bottoms contain the nonvolatile salts. In a batch column the desired product would be an intermediate fraction. The patent example describes the use of the hydroxylammonium sulfate that is treated with a NaOH/KOH mixture. The final product can contain less than 1 ppm Na and <0.4 ppm K.

While this is aimed at a continuous process for the electronics industry, it may find application where hydroxylamine is used as a highly pure chemical reagent.

Advantages

This process provides a very high purity of a versatile reagent. The product is an aqueous solution and hence should not pose a safety hazard such as the possibility of explosions from the anhydrous material.

Patent No. U.S. 7,102,029

Assignee: Mitsubishi Gas Chemical Co. Inc., Toyo Boseki Kabushiki Kaisha and Mizushima Aroma Co. Ltd., Japan

Title or Subject: Method of Crystallisation

This is another patent with a very wide-ranging title, and yet again it is aimed specifically at one product. The subject is production of terephthalic acid (TA), and this is produced on a huge scale for use in polyesters. The reason it has been included here is the interesting method used to effect crystallisation that may have applications elsewhere. The TA is obtained by oxidation of *p*-xylene and is purified by crystallisation from water. The aqueous solution is concentrated by flash evaporation to precipitate the TA crystals, and the resulting slurry is then fed tangentially to a hydrocyclone where the crystals are recovered. The hydrocyclone works by the centrifugal force causing the crystals to be thrown to the wall and collected in the base. The slurry overflows from the top and is recycled. Those readers familiar with the cyclonic vacuum cleaners will appreciate how the process works. It is easy to see how this principle could be applied to separation of crystals in other systems.

Advantages

This procedure eliminates the need for a filter that can be easily blocked.

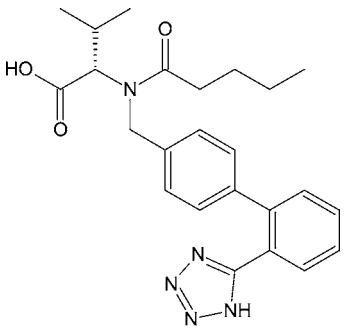
Patent No. U.S. 7,105,557

Assignee: Teva Pharmaceutical Industries Ltd., Petah Tiqva, Israel

Title or Subject: Polymorphs of Valsartan

Valsartan **78** is used to treat hypertension and especially that which is diabetes related. This patent describes methods for the production of 13 polymorphs and an amorphous form of **78**. The two claims of the patent only relate to Form I that is crystallised from MEK or EtOAc; presumably other patents may cover the remaining polymorphs. The methods used to prepare and interconvert these forms are based on using different solvents, and thermal treatments to achieve crystallisation. Extensive XRD and DSC data are given for all materials. Form I is not the most stable and can be converted to Form VIII by heating crystals of Form I that are recovered from MEK.

Valsartan



78

Advantages

The patent provides a vast range of new polymorphs that may have improved properties for preparing pharmaceutical formulations.

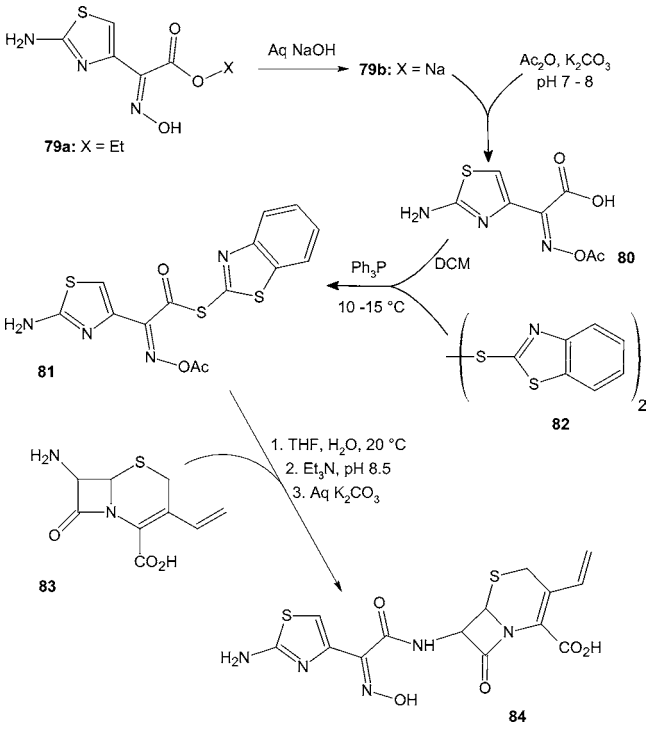
Patent No. U.S. 7, 105,659

Assignee: Aurobind - Pharma Ltd., Hyderabad, India

Title or Subject: Process for Preparing Cefdinir

Cefdinir, **84**, is a cephalosporin antibiotic having broad-spectrum activity against *Staphylococci* and *Streptococci*, two commonly found and virulent bacteria. Several methods for synthesising **84** are summarised and are said to have numerous drawbacks for commercial operation. These include low yields (<10%), very low temperature requirements, use of flammable ether solvents, use of halogenated acids and expensive reagents, and effluent disposal problems. A particular problem identified is the need for an acylating agent in the process that does not give side products or require complicated reaction procedures. The reagent identified as fulfilling the requirements is **81**. This *O*-acetyl thioester is not a novel compound and was first reported in 1989. The patent outlines the method for preparing **81** and gives more detailed information for its conversion to **84** as shown in Scheme 22. Both of the reactions are monitored by HPLC, and the final stage is stopped when <1% of **83** remains.

Scheme 22



Advantages

The use of the *O*-acetyl thioester offers an efficient method of acylation as a way of introducing the side chain onto **83** to give a good yield of the desired product.

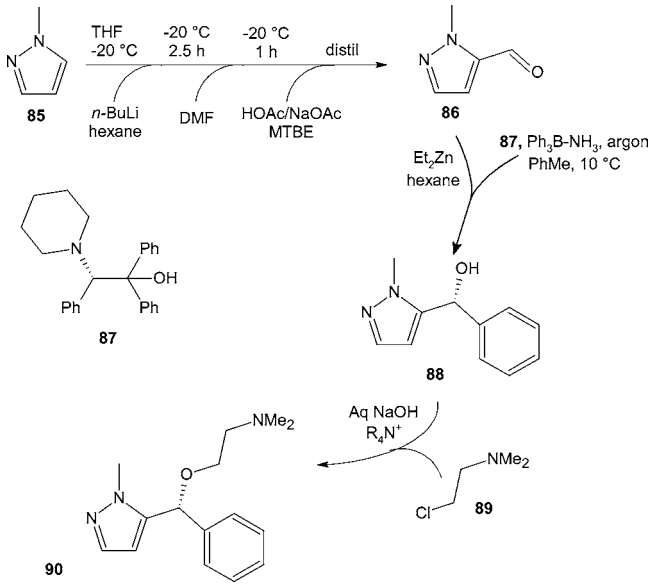
Patent No. U.S. 7,109,349

Assignee: Laboratorios Del Dr. Esteve S/A, Barcelona, Spain

Title or Subject: Process for Obtaining Cizolirtine and its Enantiomers

Cizolirtine **90** is a potent analgesic that is currently undergoing Phase II clinical trials. An obstacle in the synthesis of **90** is the separation of the enantiomers or the requirement to have an enantioselective synthesis. This patent avoids the need to resolve enantiomers and describes an enantioselective addition reaction to give a product with high ee. This is achieved by addition of a metalated phenyl reagent to an aldehyde in the presence of a chiral catalyst to give an asymmetric centre on an alcohol. It is stated that the addition of the phenyl group to the aldehyde **87** is a surprising finding in view of the fact that there are two N atoms in the ring. The process is summarised in Scheme 23 in which the first stage is preparation of the aldehyde **86** by lithiation, quenching with DMF and hydrolysis. **86** is then purified by distillation and used in the addition reaction with the phenyl zinc reagent formed from Et_2Zn, Ph_3B-NH_3. The addition is carried out in the presence of **87** as the chiral catalyst, and **88** is formed in 79% yield with an ee of 93%. The formation of the product **90** is carried out by reaction of **88** with **89** in aqueous alkaline solution containing a quaternary ammonium salt as a PTC.

Scheme 23



The patent describes a wide range of chiral catalysts that can be used plus alternative metalated reagents. For example, the reagent Et_2Zn-$Ph_2B(O)CH_2CH_2NH_2$ gave a lower yield (74%) and ee (89%). The preferred chiral ligend is **87**.

Advantages

The process provides a convenient, efficient, and stereoselective method of adding a phenyl group to the aldehyde to give high yields and ee's of the product alcohol.

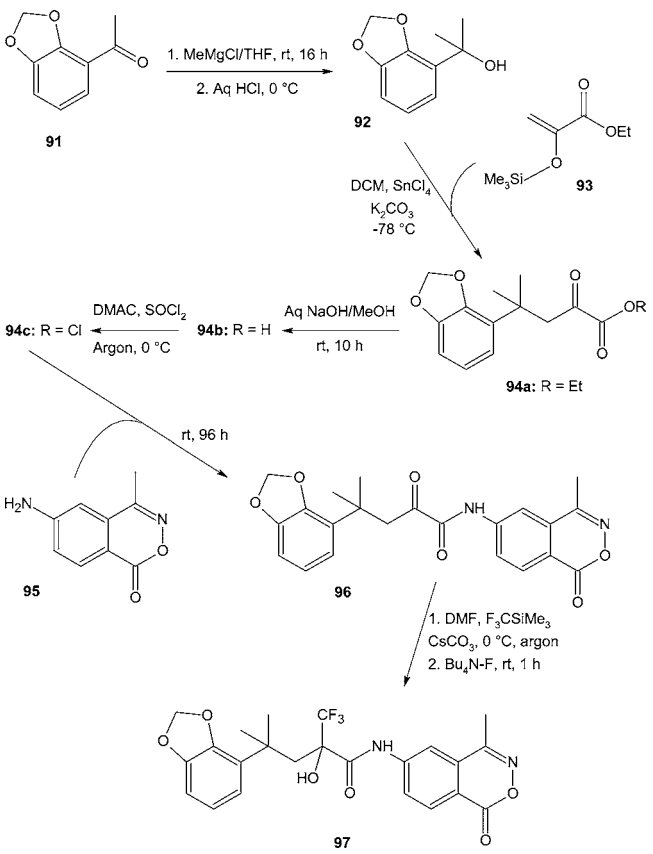
Patent No. U.S. 7,112,584

Assignee: Schering AG, Berlin, Germany

Title or Subject: Nonsteroidal Antiinflammatory Agents

There is a great deal of scientific and public interest in NSAIDs, and recently some have had to be withdrawn from use because of severe side effects such as heart attacks and strokes. Hence, this patent aims is to produce novel NSAIDs that are as active as previously known materials but do not have the same side effects. The patent describes the synthesis of a number of NSAIDs and intermediates in their production. One example is the carboxoylamino-benzoxazinone compound **97**, and a route to its synthesis is given in Scheme 24. The reaction proceeds in four distinct stages. In the first stage the alcohol **92** is produced by methylation of **91**, and in the second the oxo-ester **94a** is produced from **92** by treatment with the silyloxy ester **93** in the presence of $SnCl_4$. The third part of the route is the addition of the benzoxazine grouping to give **96**. This is carried out by treating the acyl chloride **94c** with the benzoxaninone **95** in a reaction that takes place at room temperature over 8 days. The final stage is the introduction of the CF_3 group by reaction of F_3CSiMe_3 with **96** in the presence of a base. The final product is a racemic mixture, and this is separated by chiral chromatography.

Scheme 24



There are other examples of variations on the structure of **97** where the *gem*-dimethyl groups are replaced by cyclopropyl or cyclobutyl. There are also examples where the benzodioxolone ring is replaced by benzofuran, benzox-

azole, or 4-bromophenol groups. The patent includes an extensive table of over 30 compounds that have been produced. There is also data on the activity of these compounds as inflammation inhibitors.

Advantages

The patent describes a range of novel compounds that have potential as NSAIDs.

Keith Turner

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E-mail: keith@kappa-tau.co.uk

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